

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY (Chapter I of the Patent Cooperation Treaty)

(PCT Rule 44bis)

Applicant's or agent's file reference PCT 21481Y	FOR FURTHER ACTION	See item 4 below
International application No. PCT/US2004/026012	International filing date (<i>day/month/year</i>) 11 August 2004 (11.08.2004)	Priority date (<i>day/month/year</i>) 15 August 2003 (15.08.2003)
International Patent Classification (8th edition unless older edition indicated) See relevant information in Form PCT/ISA/237		
Applicant MERCK & CO., INC.		

1. This international preliminary report on patentability (Chapter I) is issued by the International Bureau on behalf of the International Searching Authority under Rule 44 bis.1(a).

2. This REPORT consists of a total of 10 sheets, including this cover sheet.

In the attached sheets, any reference to the written opinion of the International Searching Authority should be read as a reference to the international preliminary report on patentability (Chapter I) instead.

3. This report contains indications relating to the following items:

- | | | |
|-------------------------------------|--------------|---|
| <input checked="" type="checkbox"/> | Box No. I | Basis of the report |
| <input checked="" type="checkbox"/> | Box No. II | Priority |
| <input checked="" type="checkbox"/> | Box No. III | Non-establishment of opinion with regard to novelty, inventive step and industrial applicability |
| <input type="checkbox"/> | Box No. IV | Lack of unity of invention |
| <input checked="" type="checkbox"/> | Box No. V | Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement |
| <input checked="" type="checkbox"/> | Box No. VI | Certain documents cited |
| <input checked="" type="checkbox"/> | Box No. VII | Certain defects in the international application |
| <input checked="" type="checkbox"/> | Box No. VIII | Certain observations on the international application |

4. The International Bureau will communicate this report to designated Offices in accordance with Rules 44bis.3(c) and 93bis.1 but not, except where the applicant makes an express request under Article 23(2), before the expiration of 30 months from the priority date (Rule 44bis .2).

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland	Date of issuance of this report 21 February 2006 (21.02.2006)
Facsimile No. +41 22 740 14 35	Authorized officer <div style="text-align: center; font-weight: bold;">Athina Nickitas-Etienne</div> Telephone No. +41 22 338 89 95

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

REC'D 22 DEC 2004

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To:

see form PCT/ISA/220

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WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY (PCT Rule 43bis.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.
PCT/US2004/026012

International filing date (day/month/year)
11.08.2004

Priority date (day/month/year)
15.08.2003

International Patent Classification (IPC) or both national classification and IPC
C07D401/12, C07D401/14, C07D413/14, C07D417/14, A61K31/454, A61K31/506, A61K31/497, A61P35/00

Applicant
MERCK & CO., INC.

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☒ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☒ Box No. VI Certain documents cited
- ☒ Box No. VII Certain defects in the international application
- ☒ Box No. VIII Certain observations on the international application

2. FURTHER ACTION

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:



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**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/US2004/026012

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.
 - ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).
2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:
 - a. type of material:
 - ☒ a sequence listing
 - ☐ table(s) related to the sequence listing
 - b. format of material:
 - ☒ in written format
 - ☒ in computer readable form
 - c. time of filing/furnishing:
 - ☒ contained in the international application as filed.
 - ☒ filed together with the international application in computer readable form.
 - ☐ furnished subsequently to this Authority for the purposes of search.
3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
4. Additional comments:

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/US2004/026012

Box No. II Priority

1. ☒ The following document has not been furnished:

☒ copy of the earlier application whose priority has been claimed (Rule 43*bis*.1 and 66.7(a)).

☐ translation of the earlier application whose priority has been claimed (Rule 43*bis*.1 and 66.7(b)).

Consequently it has not been possible to consider the validity of the priority claim. This opinion has nevertheless been established on the assumption that the relevant date is the claimed priority date.

2. ☐ This opinion has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rules 43*bis*.1 and 64.1). Thus for the purposes of this opinion, the international filing date indicated above is considered to be the relevant date.

3. ☐ It has not been possible to consider the validity of the priority claim because a copy of the priority document was not available to the ISA at the time that the search was conducted (Rule 17.1). This opinion has nevertheless been established on the assumption that the relevant date is the claimed priority date.

4. Additional observations, if necessary:

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/US2004/026012

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

- ☐ the entire international application,
- ☒ claims Nos. 15-17, 27-40

because:

- ☒ the said international application, or the said claims Nos. 15-17, 27-40 relate to the following subject matter which does not require an international preliminary examination (*specify*):
see separate sheet
- ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):
- ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.
- ☐ no international search report has been established for the whole application or for said claims Nos. 15-17, 27-40
- ☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:
 - the written form ☐ has not been furnished
 - ☐ does not comply with the standard
 - the computer readable form ☐ has not been furnished
 - ☐ does not comply with the standard
- ☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-bis of the Administrative Instructions.
- ☐ See separate sheet for further details

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/US2004/026012

Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims	1-40
	No: Claims	
Inventive step (IS)	Yes: Claims	1-40
	No: Claims	
Industrial applicability (IA)	Yes: Claims	1-14, 18-26
	No: Claims	

2. Citations and explanations

see separate sheet

Box No. VI Certain documents cited

1. Certain published documents (Rules 43bis.1 and 70.10)

and /or

2. Non-written disclosures (Rules 43bis.1 and 70.9)

see form 210

Box No. VII Certain defects in the international application

The following defects in the form or contents of the international application have been noted:

see separate sheet

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Claims 15-17 and 27-40 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Reference is made to the following documents:

D1: US-B-6 440 6861 (SAKOWICZ ROMAN) 27 August 2002 (2002-08-27)

D2: WO 03/049527 A (HOFFMAN WILLIAM F ; FRALEY MARK E (US); MERCK & CO INC (US); HARTMAN G) 19 June 2003 (2003-06-19)

1) Article 33(2)/(3) PCT

The application refers to compounds of the formula (I) suitable as mitotic kinesin inhibitors. Their activity was supported by the biological data provided in pages 67-70 (see in particular page 68, lines 27-28).

Reference to mitotic kinesin inhibitors was made in documents D1 and D2. However, in both documents (see D1: Figure 1 and D2: pages 73-100) the disclosed compounds are characterized by a 2-amidoalkyl-4-oxo-pyrimidine core structure, which is quite distinct in comparison to the N-(substituted piperidin-4-yl)-2,5-dihydro-1H-pyrrole-1-carboxamide core structure of the claimed compounds.

Due to the distinct structural elements of the claimed compounds with respect to the prior art and the substantiation of the claimed activity through biological data, both the novelty and the inventive merit of the present subject matter can be acknowledged.

2) Rule 67.1(iv) PCT / Article 34(4)(a)(I) PCT

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING
AUTHORITY (SEPARATE SHEET)**

International application No.

PCT/US2004/026012

For the assessment of the present claims 15-17 and 27-40 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Re Item VI

Certain documents cited

Documents:

- D3: WO 03/105855 A (ARRINGTON KENNETH L ; COX CHRISTOPHER D (US);
HOFFMAN WILLIAM F (US);) 24 December 2003 (2003-12-24)
- D4: WO 2004/037171 A (BRESLIN MICHAEL J ; COX CHRISTOPHER D (US);
COLEMAN PAUL J (US); MERCK) 6 May 2004 (2004-05-06)
- D5: WO 03/106417 A (ARRINGTON KENNETH L ; FRALEY MARK E (US);
MERCK & CO INC (US)) 24 December 2003 (2003-12-24)

can not be considered as prior art documents according to the Article 33(2) PCT, because they are published after the priority day and before the filing day of the application. However care should be taken, when entering the regional phase, because these documents could be relevant for the examination, as:

- a) D3 discloses examples 18-4, 18a-6, 18-5, 18-13, 18-14, 18-15, 18-16, 19-14, 19-15, 35-16 and 35-17 having an N-(substituted piperidin-4-yl)-2,5-dihydro-1H-pyrrole-1-carboxamide core structure and being suitable as mitotic kinesin inhibitors,
- b) D4 discloses examples 1-10, 6-12, 6-13, 7-3, page 102, 10-1, 11-1, 12-1, 13-1, 14-1, 15-1, 16-1, 16-2, 17-1, 17-2, pages 115-116, 18-2 and 30-4 having an N-(substituted piperidin-4-yl)-2,5-dihydro-1H-pyrrole-1-carboxamide core structure and being suitable as mitotic kinesin inhibitors and
- c) D5 discloses example 2-11 in page 70 acting as a mitotic kinesin inhibitor and differing from the claimed entities only in the presence of a carboxylate group instead of the carboxamido moiety.

Re Item VII

Certain defects in the international application

In claim 3 the reference to the R^c and R^d substituents is superfluous.

Re Item VIII

Certain observations on the international application

1) With respect to claims 39-40, it must be mentioned, that even if they will be reformulated to Swiss Type Form claims by entering the European Phase, they can not be considered:

a) as industrial applicable as the modulation of mitotic spindle formation and the selective inhibition of the mitotic kinesin can not be considered as therapeutic applications. The discovery, that a substance is a selective modulator / inhibitor, even if representing an important piece of scientific knowledge, still needs to find a practical application in the form of a defined, real treatment of any pathological condition in order to make a technical contribution to the art and

b) as clear (Article 84 EPC/Article 6 PCT), since no instructions, in the form of any testable criteria, are available from the patent documents or from the common general knowledge allowing the skilled person to recognise, which conditions fall within the functional definition e.g. **any** condition susceptible of being improved or prevented by the modulation of mitotic spindle formation and the selective inhibition of the mitotic kinesin, and accordingly within the scope of the claims.

The reason for the necessity of this clarification is, that a claim referring to a condition to be treated, which is functionally defined, would not be limited to the treatment of said specified condition (here cancer), but by contrast embraces an undefined number of conditions all allegedly capable of being improved or prevented by the modulation of mitotic spindle formation / the selective inhibition of the mitotic kinesin. Under these circumstances the independent claim can only be regarded as clear if means are available to the skilled person for assessing whether or not an additional condition not expressly filed in the application but nevertheless affected by the administration of the said compounds is comprised in the scope of the claim.

2) The reference in claims 19-26, 28-29 and 31-38 to inhibitors of proteasome, aurora kinase etc. is beyond any reasonable generalization, as these claims embrace an undefined number of structurally undefined compounds.

3) Furthermore the limited variations in the substitution pattern of the claimed compounds in the disclosed examples, do not justify the breadth of compound claims 1-4 (**Article 6 PCT: fully supported by the description**).

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING
AUTHORITY (SEPARATE SHEET)**

International application No.

PCT/US2004/026012

The applicant is entitled to claim only obvious modifications of what was described (close related variations), since the claims should represent a reasonable generalisation of the examples given in the description: the technical features stated in the description/examples as being essential features of the invention described must be the same as those used to define the invention in the claims. The reason for that is that the problem to be solved **should be solved by the whole scope of the claimed subject matter** (every compound falling within its scope) and not just by individual compounds- especially since the problem may be seen in the provision of compounds acting on a biological system (i.e. on a system depending upon very different parameters). If this were not the case, an invention could arbitrarily be broadened to any limit without consideration, whether the compounds are actually solving the problem underlying the invention.